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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/934,207	08/21/2001	Imre Kovesdi	213187	8411

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
1632	8

DATE MAILED: 04/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/934,207	Applicant(s) Kovesdi et al.
	Examiner Scott D. Priebe, Ph.D.	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 36-55 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 36-55 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed 8/21/01 has been entered. Claims 1-35 have been cancelled. Claims 36-55 have been added.

Information Disclosure Statement

References AK, AR, AV and AW were considered only with respect to their English abstracts.

Claim Objections

Claims 46-55 are objected to because of the following informalities: Claims 46-55 depend from claims 36-45, respectively, which are directed to a composition of adenoviral vectors. To maintain consistency, the phrase "the adenoviral vector is" in line 1 of each of claims 46-55 should be replaced with --the adenoviral vectors are--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly directed to "pharmaceutical" compositions comprising adenoviral vectors. The limitation of the claimed compositions to "pharmaceutical" compositions is interpreted as a statement that the claimed compositions have the intended use as a pharmaceutical, i.e. for treatment. The specification teaches that the adenoviral vectors are to be used either in gene therapy or for vaccination. The specification teaches three general therapeutic applications, gene therapy by expression of an exogenous protein or antisense RNA or vaccination by expression of an immunogenic peptide. With the exception of expressing CFTR for treating cystic fibrosis, no specific therapeutic application is disclosed. The specification provides no working examples of these methods, and provides very limited guidance, relying wholly on the prior art.

With respect to gene therapy, whether by expression of a protein or antisense RNA, at the time the application was filed the art of administering any type of expression vector to an individual so as to effectively transfect targeted cells in said individual and provide a tangible therapeutic benefit was poorly developed, unsuccessful and unpredictable. The NIH *ad hoc* committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims ...," and that "significant problems remain in all basic aspects of gene therapy" (p. 1)." In a review article published in Scientific American in June 1997,

Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide." A particular problem that arises in attempting to use adenovirus-based vectors for gene therapy is that the structural proteins of adenovirus vectors elicit a host humoral immune response which interferes with the efficacy subsequent administrations of the vector (Crystal, p. 16, middle column; Trapnell et al., pp. 621-622; Schulick et al., pp. 209-216; DeMatteo et al., pp. 315-319). The courts have held that the scope of the claims must be commensurate with the scope of enablement provided to the skilled artisan by the specification, that sufficiency of the application under 35 U.S.C. § 112, first paragraph, must be judged as of its filing date. See *Ex parte Hitzeman*, 9 USPQ2d 1822, 1823 (PTO BPAI, 1988). In view of the recognized obstacles to successful use of adenovirus vectors to provide therapeutic benefit *in vivo*, and the high degree of unpredictability in the art of gene therapy at the time the application was filed, as discussed above, one skilled in the art at the time the application was filed would not have considered the descriptions of vectors and cell lines given in the examples to be correlative with successful operation of the claimed gene therapy method.

With respect to vaccines, while the prior art teaches the successful use of replication competent adenoviral vaccine vectors, the consequence of rendering the vaccine vector replication defective was not known in the prior art. Nor can one predict *a priori* whether the inability of the adenoviral vector to replicate upon infection of the mammal would affect its

function as a carrier and adjuvant for the antigenic or immunogenic vaccine polypeptide expressed by the vector. It is thought that adenoviral infection potentiates the immune response to the antigenic or immunogenic peptide or protein of interest, due to the immunogenicity of the adenoviral proteins. Replication competent adenoviral vaccine vectors are able to expand the initial infection, i.e. reproduce in the cells initially infected to produce more infectious adenovirus, and infect additional cells. With the adenoviral vectors of the invention, only cells initially infected would produce virally encoded proteins, including the antigenic or immunogenic peptide for the vaccine. In addition, the multiple deleted vectors of the invention would be expected to produce little or no adenoviral proteins in the infected cells, as compared to a replication competent adenoviral vector of the prior art. Therefore, it is not clear that one would be able to use replication defective adenoviruses as vaccine vectors simply as a replacement for the replication competent adenoviral vectors of the prior art adenoviral vaccine vectors without undue experimentation, as indicated in the specification.

Given the breadth of the claims, which encompass a wide range of gene therapy or vaccine vector types, compositions, and methods, to treat a wide range of pathologies in any type of animal or in a human; given the unpredictability of the operation of the claimed invention as discussed above; and given the absence of guidance or correlative example in the specification showing how use the claimed invention successfully in a living animal or human as discussedabove, undue experimentation would have been required by one skilled in the art at the

time the application was filed to use the claimed method. This rejection would be overcome by amending the claims by deleting "pharmaceutical" from claim 36, line 1.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 36-55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-31 and 49-62 of U.S. Patent No. 5,851,806. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims embrace compositions of the adenoviral vectors of the '806 patent, see in particular claims 5, 25-31, and 62. The specification of the '806 patent discloses that compositions of the adenoviral vectors are intended for *ex vivo* or *in vivo* use requiring a pharmaceutically acceptable composition. The intended use of the instant compositions as a

pharmaceutical does not distinguish the instant compositions from pharmaceutically acceptable compositions of the patent.

Claims 36-55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 5,994,106. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are directed to essentially the same subject matter. The stocks of the '106 patent are compositions containing the claimed adenoviral vectors, and the specification of the '106 patent discloses that such stocks are intended for *ex vivo* or *in vivo* use requiring a pharmaceutically acceptable composition. The intended use of the instant compositions as a pharmaceutical does not distinguish the instant compositions from pharmaceutically acceptable compositions of the patent.

Claims 36-55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 66-78 of copending Application No. 09/321,797. Although the conflicting claims are not identical, they are not patentably distinct from each other because the system and methods of the '797, when read in light of that specification, are specifically designed to produce the compositions (i.e. RCA-free stocks) of the instant claims, and cannot be practiced without making the compositions. The specification of the '797 application discloses that such stocks produced with the claimed system

and by the claimed methods are intended for *ex vivo* or *in vivo* use requiring a pharmaceutically acceptable composition. The intended use of the instant compositions as a pharmaceutical does not distinguish the instant compositions from pharmaceutically acceptable compositions of the patent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. However, the '797 application is due to issue as U.S. Patent No. 6,482,616 on 11 Nov. 2002, at which time this rejection will no longer be provisional. Rather it will be over claims 1-13 of the '616 patent.

Claims 36-55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-38, 49, 51-54, 68-70, 72-76, 90, 91, 93-100, and 102-114 of copending Application No. 09/261,922. Although the conflicting claims are not identical, they are not patentably distinct from each other because the system and methods of the '922 are specifically designed to produce compositions (stocks) of the same adenoviral vectors of the instant claims, and cannot be practiced without making the compositions. The specification of the '922 application discloses that such stocks produced with the claimed system and by the claimed methods are intended for *ex vivo* or *in vivo* use requiring a pharmaceutically acceptable composition. The intended use of the instant compositions as a pharmaceutical does not distinguish the instant compositions from pharmaceutically acceptable compositions of the patent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

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